REMARKS

Applicant filed the present Application on November 22, 2000 with claims 1-59. On March 27, 2002, the USPTO mailed the first office action with a restriction requirement. The Examiner requested that the Applicant elect a group for prosecution from the following groups:

I. Claims 1-33 and 59 are drawn to a composition comprising ex vivo expanded cells, classified in class 424, subclass 93.71.

II. Claims 34-44, 52-58 are drawn to a method of treating patients suffering from cancer, classified in class 424, subclass 93.1.

III. Claims 45-47 are drawn to a method of preparing a composition comprising ex vivo expanded cells, classified in class 435, subclass 325.

IV. Claims 48-51 are drawn to a method of ex vivo expansion of EAT cells, classified in class 435, subclass 420.

On September 27, 2002 previous counsel responded to the restriction requirement with the Applicant electing the claims of Group I. On December 18, 2002 the Examiner mailed the second office action with claims 1-59 pending (claims 34-58 were withdrawn as non-elected and claims 1-33 and 59 were elected).

On June 18, 2003 previous counsel mailed a "Reply" in which claims 2, 5, 9-13, 23, 26-33, and 59 were cancelled and new claims 60-63 were added. In the Reply, non-elected claims 34-58 were indicated as cancelled in the listing of the claim amendments, but the Remarks section of that Reply did not indicate that claims 34-58 are cancelled. In the Action, the Examiner requests clarification. In response, it is the Applicant's intent to request rejoinder of certain non-elected claims through operation of M.P.E.P. §821.04. For this reason, Applicant

indicates in the present Amendment that claims 34-58 are withdrawn and not cancelled. Despite this clarification, should the Examiner consider claims 34-58 to be cancelled through operation of Applicant's June 18, 2003 Reply, applicant hereby reserves the right to reinstate and rejoin those claims at an appropriate time. Therefore, by action off the June 18, 2003 Reply, claims 2, 5, 9-13, 23, 26-33, and 59 are cancelled, claims 34-58 are withdrawn and claims 1, 3-4, 6-8, 14-22, 24-25, 60-63 are pending.

In response to the Action dated September 9, 2003, claims 3, 4, 7, 8, 14-19, 62, and 63 are hereby cancelled. Applicant also requests that claims 64-92 be added for examination. 1, 6, 20-21, 24, 25, 60, and 61 are currently amended. No new matter is added by the amendments and new claims presented herein. The following claims are now pending: 1, 6, 20-22, 24, 25, 60, 61, and 64-92. Rejections raised in the final office action will be addressed in detail *infra*.

Claims

Rejections Under 35 U.S.C. § 112, first paragraph

The Examiner has rejected claims 1, 3-4, 6-8, 14-22, 24-25, and 60-63 under 35 U.S.C. § 112, first paragraph for allegedly failing to comply with the written description requirements. Specifically, the claims are rejected for purportedly introducing new matter. With particular regard to claim 1, the Examiner purported that "the limitation of comparing CIK selectivity to unstimulated PBMCs is not supported in the specification or in the claims as originally filed."

Applicant respectfully disagrees with the Examiner. Without intending to relinquish any scope of claims 1, 3-4, 6-8, 14-22, 24-25, and 60-63, however, Applicant respectfully request that the Examiner cancel claims 3, 4, 7, 8, 14-19, 62 and 63. In light of the cancellation of these

claims, the written description and new matter rejection has been rendered moot with regard to those particular claims.

With regard to claim 1, Applicant complies with the Examiner's request by removing the limitation of comparing CIK selectivity to unstimulated PBMCs solely for clarity and without prejudice or any qualification as to whether the limitation is supported or unsupported by the specification. Support for the language of claim 1, and for claims dependent therefrom, can be found throughout the specification of the present Application (see, for example, page 2, line 22 through page 8, line 16; page 9, line 15 through page 13, line 25; page 14, line 21 through page 17, line 4; and page 21, line 3 through page 31, line 21). In complying with Examiner's request, Applicant believes the claims dependent on amended claim 1 and amended claim 1 are in proper form for allowance. Therefore, Applicant respectfully requests that the Examiner withdraw this rejection.

Rejections Under 35 U.S.C. § 112, second paragraph

The Examiner has rejected claims 14 and 15 under 35 U.S.C. § 112, second paragraph for indefiniteness for improper dependency. For reasons of clarity, unrelated to this rejection, claims 14 and 15 are cancelled, rendering this rejection moot.

Rejections Under 35 U.S.C. § 102(b)

The Examiner has rejected claims 1, 14-21 and claims 60-63 under 35 U.S.C. § 102(b) for anticipation by Lu *et al.* In particular, the Examiner states, "Lu *et al* disclose a composition comprising CIK cells and further disclose the administration of said composition to a SCID mouse animal model. Lu *et al* further teach that the CIK cells generated and administered are capable of generating an antitumor response. The specification of the instant application

discloses that CIK cells are generated by a method of adding cytokines to peripheral blood lymphocytes (PBL in a specific manner (see example 1), of which is identical to the method of preparing CIKs taught by Lu *et al.*" *See* page 3 of the Action.

First, claims 1, 60 and 61 have been amended herein to be drawn to a "population of cytotoxic lymphocytes" as supported by the specification, as stated *supra* (claims 14-19 and 62-63 have been cancelled). Second, the Examiner's argument that an identical method is taught by Lu *et al* is inaccurate. Lu *et al* teaches that "[t]o generate CIK cells, 1000 U/ml human rIFN-γ . . . .were added on day 1. After 24 h of incubation, 50 ng/ml mAB against CD3 . . . , 300 IU/ml rIL-2 . . . and 100 U/ml rIL-1α . . . .were added" (source citations omitted). *See*, Lu *et al* at page 1688. The cell population of the composition of the invention is generated in part as follows as stated in the specification on page 21, lines 17-24: "The enriched cell population was stimulated at day 0 by the addition of 1000 IU ml recombinant human interferon gamma (rhu γ-IFN) . . . . On day 1, the cell population was stimulated with (1) 50 ng/ml of the soluble anti-human CD3 monoclonal antibody OKT-3 . . . .and; (2) 300 IU/ml of recombinant human interleukin-2 (rhu IL-2) " (source citations omitted). The methods described in the specification do not include the addition of rIL-1α to create the cell populations of the composition of the invention.

In addition, Lu *et al* uses an open flask system, as commonly done in the art, to grow the CIK cells, whereas the methods of the invention use a closed bioreactor. Lu *et al* states, "fresh $CD3^+$ $CD56^-$ T cells and $CD3^+$ $CD56^-$ NK cells are cultured in complete medium at 37°C, 5% CO_2." The specification of the invention states, "EAT cells are grown with agitation and/or aeration of the culture, e.g., in 'closed' culture system, such as a bioreactor. Thus, they can grown, e.g., with the use of rocking platforms, tumblers, stirred bio-reactors without electrodes, advanced bioreactors, especially with the use of electrodes (e.g. but not limited to pO2, pCO2,

RPM, temperature, cell density/OD) inserted into the culture chamber. They are preferably grown with continued feeding and harvesting. . . ." *See* Specification at pages 11 lines 5-20. Lu *et al* does not teach the use of a closed bioreactor system. Furthermore, Figure 2B of the specification demonstrates the difference between bioreactor grown cells compared to standard flask grown cells.

Therefore, Applicant respectfully disagrees with arguments raised by the Examiner on basis that the "method of generating the CIKs taught by Lu *et al* is identical to that taught in the instant specification." *See* pages 3-4 of Final Office Action mailed September 9, 2003. Because the methods of preparing the composition of the invention is in fact different from that described by Lu *et al*, Applicant must disagree with the Examiner's statement that "the CIKs taught by Lu *et al* would also have damaging affects on tumor associated vasculature." Lu *et al* makes no mention of this characteristic nor do they even allude to that possibility. Because the method disclosed in Lu *et al* is different from the method claimed, the teachings of Lu *et al* cannot support a rejection under 35 U.S.C § 102.

Further, the Examiner's statement that "Lu *et al* further teach that the CIK cells generated and administered are capable of generating an antitumor response," is a broad overgeneralization. Lu *et al* specifically teaches use of the "SCID mouse model of human lymphoma to evaluate the antitumor effects of CIK vs. LAK cells." *See* Lu *et al*, p. 1689. In particular, Lu *et al* uses SU-DHL4 cells, a human B lymphoma cell line and makes no mention whatsoever of the use of CIK cells with other cancer types. The present invention, however, can be used for many different types and kinds of cancers as stated in the specification on page 6, lines 23 to page 7, line 19, including, but not limited to, "lymphomas and leukemias . . .solid tumors . . . gonadal cancers . . .airway cancers. . . gastrointestinal cancers . . ."etc. Furthermore, Lu *et al* does not teach

anything with regard to the invention's ability to "selectively damage tumor associated vasculature cells.

The Examiner also states, "because PBLs or PBMCs are unstimulated cells that have no cyctotoxic effects or are anergic (see page 2), in general, the CIK's taught by Lu *et al* would also have more activity when compared to unstimulated cells. Thus the percentage of activity claimed is an inherent property of all stimulated cells whether they have preference to tumor cells, endothelial cells or to both."

Applicant respectfully disagree with the Examiner, however, Applicant, complies with the Examiner's request by removing the limitation of comparing CIK selectivity to unstimulated PBMCs without prejudice or any qualification as to whether the limitation is supported or unsupported by the specification. Therefore, the Examiner's argument is rendered moot by the removal of this limitation from the claims.

Applicant thereby requests that the Examiner withdraw his rejection on the basis of 35 U.S.C. § 102(b).

Applicant believes that claims 1, 6, 20-22, 24, 25, 60, 61, and 64-92 define over the prior art of record and are in proper form for allowance. Applicant respectfully requests allowance of

claims 1, 6, 20-22, 24, 25, 60, 61, and 64-92. Applicant also requests that the Examiner call the undersigned to discuss any additional questions or concerns with respect to the above-referenced patent application.

Respectfully submitted,

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